REMARKS

I. Status of the Claims and Previous Rejections.

Claims 88–100 and 102–112 are pending in the application. Claims 88–100, 104, 106–110, and 112 have been withdrawn from consideration as drawn to non-elected species. Therefore claims 102, 103, 105, and 111 are pending and currently under examination.

Claims 88 and 102 have been amended to recite ". . . such that the secondary and tertiary structure of the self protein is preserved to a large extent[.]" Support for that amendment can be found in the specification as-filed, for example, at page 3, lines 26-30. Thus the claim amendments are fully supported and add no new matter.

With respect to all claim amendments, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to prosecute any presently excluded claim embodiments in a future continuation and/or divisional application.

Applicants gratefully acknowledge the Examiner's withdrawal of: (1) the prior rejection of claims 102, 103, 105, and 111 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement; and (2) the prior rejection of claims 102, 103, 105, and 111 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

II. Telephone Interview

Applicants thank Examiner Schwadron for extending the courtesy of a telephone interview with Applicants' representative David Hoffman on April 27, 2011. Applicants note that an Examiner Interview Summary pursuant to MPEP § 713.04 and 37 C.F.R. § 1.2 has not yet been posted in the image file wrapper on the USPTO Patent Application Information Retrieval ("PAIR") system. In the interest of expediting prosecution, however, Applicants summarize below their

understanding of the topics discussed with the Examiner so that a Statement of the Substance of Interview need not be filed separately.

Applicants' representative briefly discussed and sought to clarify the Examiner's positions regarding the outstanding written description, indefiniteness, and obviousness rejections. In particular, Applicants' representative discussed: (1) potential claim amendments to address the Examiner's allegation that the specification lacks written description support for the language of the pending claims; (2) strategies for addressing the alleged indefiniteness of the pending claims; and (3) potential submission of additional data to address the Examiner's allegation that Applicants' showing of unexpected results was not commensurate in scope with the pending claims.

Applicants gratefully acknowledge the helpful comments provided by Examiner Schwadron during the interview which are reflected in the current response.

III. Rejection under 35 U.S.C. § 112, first paragraph (Written Description).

The Examiner has rejected claims 102, 103, 105, and 111 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. Applicants amended claim 102 to recite that "the secondary and tertiary structure of the self protein *is essentially preserved*" in the Amendment and Reply to Office Action filed November 24, 2010 (emphasis added). The Examiner alleged that "[t]here is no support for the new limitation recited in claim 102" because the specification discloses "that the secondary and tertiary structure *are preserved to a large extent*." Office Action mailed February 17, 2011, section 4, page 2 (emphasis added).[1] Consequently, the Examiner alleged that "[t]he disclosure provided in the specification is not commensurate in scope

[1] Claims 103, 105, and 111 all depend directly or indirectly from rejected claim 102, and therefore incorporate by reference all elements of that claim, although they do not recite the term "essentially preserved" to which the Examiner objects. Applicants assume that claims 103, 105, and 111 have been rejected under 35 U.S.C. § 112, second paragraph for that reason, and note therefore that all arguments relating to amended claim 102 complying with the written description requirement also apply to claims 103, 105, and 111.

with the claimed invention (aka the claimed invention constitutes new matter)." *Id.* According to the Examiner, the phrase "the secondary and tertiary structure of the self protein is essentially preserved" is not sufficiently close in meaning to the statement in the specification asserting that "the secondary and tertiary structure [of the self-protein] are preserved to a large extent" to permit Applicants to rely on the latter disclosure as written description support for a claim reciting such a phrase.

Applicants respectfully traverse. As Applicants have noted previously, to assess whether a claim satisfies the written description requirement, the fundamental factual inquiry "is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." MPEP § 2163.02 (citing *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)). *Importantly, the subject matter of the claim need not be described using exactly the same terminology in order for the disclosure to satisfy the written description requirement.* MPEP § 2163.02.

Nevertheless, without acquiescing to the rejection, and solely to expedite prosecution, Applicants have amended claim 102 to recite ". . . such that the secondary and tertiary structure of the self protein is preserved to a large extent[.]"[2] Support for that amendment can be found in the specification as-filed, for example, at page 3, lines 26-30.

Applicants believe that that amendment obviates the rejection of claims 102, 103, 105 and 111 for allegedly failing to comply with the written description requirement of 35 U.S.C. § 112, first paragraph, and therefore ask that it be withdrawn.

[2] Applicants have correspondingly amended withdrawn claim 88.

IV. Rejection under 35 U.S.C. § 112, second paragraph (Indefiniteness).

The Examiner has rejected claims 102, 103, 105, and 111 under 35 U.S.C. § 112, second paragraph as allegedly indefinite. In particular, the Examiner alleged that the phrase "the secondary [] and tertiary structure of the self-protein is essentially preserved" renders claim 102 indefinite because "it is unclear what changes to the secondary structure would or would not be encompassed by the aforementioned term."[3] Office Action mailed February 17, 2011, section 7, page 3. As in several previous Office Actions, the Examiner again asserted that "it is unclear if this term encompasses changes at the physical/chemical level (*eg.* crystal structure) or simply functional changes (*eg.* still immunogenic antigen as evidenced by antibody binding by antibodies specific for unmodified antigen)" and further noted "[i]f the term is interpreted as encompassing changes at the physical/chemical level, it is unclear as to what deviations from the normal crystal structure would or would not be encompassed" by the disputed claim term. *Id.*

If instead the disputed claim term is interpreted as encompassing "simply functional changes," however, as Applicants submit that it would be interpreted by one skilled in the art, the nature and scope of the functional changes encompassed by the term would be clear from the plain language of the claim as explained in more detail below. Indeed, Applicants are unsure why the Examiner continues to raise this hypothetical concern, because previous responses have clearly asserted that the disputed claim term encompasses functional changes to the self-protein analogue.

For at least the reasons discussed below, Applicants respectfully traverse.

[3] Claims 103, 105, and 111 all depend directly or indirectly from claim 102, and therefore incorporate by reference all elements of that claim, although they do not themselves recite the phrase "the secondary [] and tertiary structure of the self-protein is essentially preserved" to which the Examiner objects. Applicants assume that claims 103, 105, and 111 have been rejected under 35 U.S.C. § 112, second paragraph for that reason, and note therefore that all arguments relating to the definiteness of amended claim 102 also apply to claims 103, 105, and 111.

A. Amended claim 102 will likely raise similar issues under 35 U.S.C. §112, ¶2, as pending claim 102.

Applicants note that the formulation of claim 102 rejected as allegedly indefinite in the current Office Action recites "such that the secondary and tertiary structure of the self-protein *is essentially preserved*[.]" While Applicants have in this response amended claim 102 to recite ". . . such that the secondary and tertiary structure of the self protein is preserved to a large extent[,]" to address the Examiner's written description rejection under 35 U.S.C. § 112, ¶1 (as discussed in section III. above), during the telephone interview of April 27, 2011, the Examiner indicated that newly-amended claim 102 would likely raise similar issues under 35 U.S.C. § 112, ¶2 for alleged indefiniteness. Consequently, although Applicants' response addresses the allegations of the current Office Action relating to the "such that the secondary and tertiary structure of the self-protein is essentially preserved" language, those arguments apply equally to the currently amended claims reciting the "secondary and tertiary structure of the self-protein is preserved to a large extent" language, and the two phrases are used interchangeably throughout this response.

B. Assessing compliance with the definiteness requirement of 35 U.S.C. § 112, second paragraph.

When reviewing a claim for compliance with the definiteness requirement of 35 U.S.C. § 112, second paragraph, "the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph, by providing clear warning to others as to what constitutes infringement of the patent." MPEP § 2173.02 (citing *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000)).

Definiteness of claim language under 35 U.S.C. § 112, second paragraph, is not analyzed in a vacuum, but in light of the content of the particular application disclosure, the teachings of the prior art, and the claim interpretation that would be given by one possessing the ordinary level of skill in

the pertinent art at the time the invention was made. MPEP § 2173.02. The essential inquiry focuses upon "whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity." *Id.* Acceptability of claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification. *Id.* (citing *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986)). Accordingly, "a claim term that is not . . . defined in the specification is not indefinite if the meaning of the claim term is discernible." *Id.* (citing *Bancorp Services, L.L.C. v. Hartford Life Ins. Co.*, 359 F.3d 1367, 1372, 69 USPQ2d 1996, 1999-2000 (Fed. Cir. 2004)).

C. Claims 102, 103, 105, and 111 comply with the definiteness requirement of 35 U.S.C. § 112, second paragraph.

Applicants respectfully assert that claims 102, 103, 105 and 111 comply with the definiteness requirement of 35 U.S.C. § 112, ¶2 because the plain language of the claims apprises one of ordinary skill in the art reading the claims as a whole of their scope, thereby satisfying the notice function required by statute. Furthermore, the prosecution history of this application shows that the Examiner clearly understands the meaning of the claims in the same way as would one skilled in the art. Numerous office communications have made clear that the Examiner understands the requirement "to essentially preserve the overall tertiary structure" of a target protein after inserting heterologous T helper cell epitopes to mean preserving the three dimensional structure sufficiently that the chimeric protein retains its immunogenicity (*i.e.*, the ability to function as an immunogen). Finally, the Examiner's understanding is supported by three declarations from scientists of ordinary skill in the art, each independently concluding the disputed claim language is definite.

1. The pending claims as amended comply with the definiteness requirement of 35 U.S.C. § 112, second paragraph because the plain language of the claims apprises one skilled in the art reading the claims as a whole of their scope.

Applicants respectfully assert that amended claim 102 complies with the definiteness requirement of 35 U.S.C. § 112, second paragraph, because the plain language of the claims apprises one skilled in the art reading the claims as a whole of their scope. The disputed claim language therefore serves the notice function required by statute.

Indeed, the plain language of amended claim 102 makes clear that "functional changes"—adopting the Examiner's terminology—to the secondary and tertiary structure of a self-protein analog would be encompassed by the phrase "the secondary and tertiary structure of the self-protein is preserved to a large extent[.]" Amended claim 102 recites:

> [a] method for inducing autoantibodies against a self-protein in a subject, said method comprising:
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> administering to the subject an analog of the self-protein made by molecular biological means, wherein said analog is made by substituting one or more peptide fragments in the self-protein with a corresponding number of immunodominant foreign T-cell epitopes selected from ovalbumin, hen egg lysozyme, tetanus toxoid, or diphtheria toxoid T-cell epitopes,
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> such that the secondary and tertiary structure of the self protein is preserved to a large extent; *such that said analog induces an autoantibody response as evidenced by antibody binding to the unmodified self-protein*

(emphasis added). Thus, the secondary and tertiary structure of a self-protein analog is preserved to a large extent where: (1) the self-protein analog induces an autoantibody response in a subject; and (2) the induced autoantibodies bind to the corresponding unmodified self-protein. The plain language of claim 102 therefore apprises one skilled in the art of its scope—the secondary and tertiary structure of a self-protein is preserved to a large extent when those two criteria are satisfied—and thereby serves the notice function required by statute.

Because the plain language of the claim makes clear that the disputed claim term encompasses 'functional changes' to the secondary and tertiary structure of a self-protein and not 'changes at the physical/chemical level,' it is not necessary to define the nature and scope of any changes to the secondary and tertiary structure of the self-protein.

For at least this reason, Applicants assert that claims 102, 103, 105, and 111 comply with the definiteness requirement of 35 U.S.C. § 112, second paragraph and therefore ask that the rejection be withdrawn.

2. The prosecution history of this application shows that the Examiner clearly understood the scope of the pending claims to be definite in the same way as would a person skilled in the art.

Moreover, the extensive prosecution history of this application shows that the Examiner clearly understood the meaning of the pending claims to be definite in the same way as would a person skilled in the art, as shown by numerous office communications issued during prosecution.

Throughout well over a decade of prosecution,[4] the Examiner has repeatedly alleged that variations on the claim language "the secondary and tertiary structure of the self-protein is essentially preserved" or "the tertiary structure of the self-protein is essentially preserved" rendered the claims indefinite because it is unclear what changes to the secondary and/or tertiary structure would or would not be encompassed by that claim language, and because it is unclear whether that phrase encompassed changes at the physical/chemical level (*e.g.*, changes to the crystal structure) or simply functional changes (*e.g.*, such that the protein remains immunogenic as shown by binding of antibodies specific for the unmodified protein). *See, e.g.*, (1) Office Action mailed August 22, 1996, at section 22, page 6; (2) Office Action mailed April 21, 1997, at section 22, pages 4-5; (3) Office Action mailed July 14, 1999, at section 8, page 3; (4) Office Action mailed May 2, 2000, at section 4, page 2; (5) Advisory Action mailed February 21, 2001, at section 6, pages 2-3; (6) Office Action mailed November 27, 2001, at section 5, pages 3-5; (7) Office Action mailed January 11, 2007, at section 9, page 5; (8) Office Action mailed October 18, 2007, at section 6, pages 5-9; (9) Office Action mailed October 16, 2008, at section 6, pages 5-7; (10) Office Action mailed October 30,

[4] According to the prosecution file history, this application has been before Examiner Schwadron since at least August 22, 1996.

2009, at section 7, pages 7-8; (11) Office Action mailed August 4, 2010, at section 6, page 3; and (12) Office Action mailed February 17, 2011, section 7, page 3.

Significantly, at the same time the Examiner repeatedly rejected the claims as allegedly indefinite, he explained precisely what he understood those same claims to mean when applying certain prior art references in a series of rejections under 35 U.S.C. §§ 102 and 103. Because the Court of Appeals of the Federal Circuit has held that patent examiners are "persons of scientific competence in the fields in which they work" and their findings are "informed by their scientific knowledge, as to the meaning of prior art references to persons of ordinary skill in the art[,]" *the Examiner's interpretation of the claims when applying certain prior art references during prosecution shows that the Examiner clearly understood the scope of the disputed claim language to be definite, in the same way as would a person of ordinary skill in the art, despite the repeated assertions of indefiniteness.* MPEP § 2141 (quoting *In re Berg*, 320 F.3d 1310, 1315, 65 USPQ2d 2003, 2007 (Fed. Cir. 2003)).

For example, the Examiner rejected claims containing the disputed claim term under 35 U.S.C. § 102(b) in an Office Action mailed July 14, 1999, alleging that:

> Russell-Jones et al. teach that the Trat peptide is inserted such that the protein still functions as an immunogen. *The Trat peptide has been inserted into the immunogen in such a manner as to 'essentially preserve the overall tertiary structure', because the ability of the immunogen to function as an immunogen is maintained* (see page 8, first complete paragraph).

Office Action mailed July 14, 1999, section 10, page 4 (emphasis added). Thus, the Examiner clearly understood the requirement "to essentially preserve the overall tertiary structure" of a target protein after inserting heterologous T helper cell epitopes to mean preserving the three dimensional structure sufficiently that the chimeric protein retained its immunogenicity (*i.e.*, the ability to function as an immunogen). The Examiner repeated that argument essentially verbatim in several additional rejections under 35 U.S.C. §§ 102(b) and 103(a) issued in the Office Action mailed May 2, 2000, at section 6, page 3; the Advisory Action mailed February 21, 2001, at section 8, page 4; the

Office Action mailed November 27, 2001, at section 7, pages 5-6; the Office Action mailed January 11, 2007, at section 11, page 6; the Office Action mailed October 18, 2007, at section 8, pages 9-10; the Office Action mailed October 16, 2008, at section 9, page 8; and the Office Action mailed October 30, 2009, at section 13, pages 10-12.[5]

Taken together, the numerous office communications issued during the course of more than ten years of prosecution in this application unambiguously show that the Examiner clearly understood the scope of the disputed claim language to be definite, in the same way as would a person of ordinary skill in the art, despite the repeated allegations of indefiniteness. *Applicants respectfully assert that the prosecution file history clearly shows the claims as amended comply with the definiteness requirement of 35 U.S.C. § 112, second paragraph, because one skilled in the art reading claim 102 as a whole would be apprised of its scope and the disputed claim language therefore serves the notice function required by statute.*

For at least this additional reason, Applicants respectfully assert that amended claims 102, 103, 105, and 111 comply with the definiteness requirement of 35 U.S.C. § 112, second paragraph, and therefore ask that the rejection be withdrawn.

3. Three separate declarations have also shown the pending claims to be definite because one of ordinary skill in the art understands the scope of the claims in light of the specification.

Finally, the definiteness of the claim language is further supported by three separate declarations under 37 C.F.R. § 1.132 submitted during prosecution, each independently concluding that the disputed claim term was definite and confirming the Examiner's understanding of the claim.

[5] Significantly, the Examiner eventually realized that several previous Office Actions repeatedly provided a clear definition for the disputed claim term while at the same time rejecting it over and over again as allegedly indefinite, but not until the Office Action mailed August 4, 2010. In an attempt to reconcile those contradictory positions after maintaining them consistently throughout more than a decade of prosecution, the Examiner qualified the discussion of the Russell-Jones reference cited in a maintained rejection under 35 U.S.C. § 103(a) by stating: "[w]hilst the term 'secondary structure of the pathogenic self-protein is essentially preserved' is indefinite as per above, for the purposes of this rejection it will be assumed the aforementioned limitation encompasses the ability of the immunogen to function as an immunogen[]." Office Action mailed August 4, 2010, at section 8, page 4.

Applicants submitted the Declaration of Professor Sven Frøkjaer, Ph.D.[6] (hereinafter "the Frøkjaer Declaration"), with a Preliminary Amendment filed August 19, 1998. As Dr. Frøkjaer explained, "it is important to preserve the overall tertiary structure of the original self-protein in order to optimize its therapeutic effect. Indeed, a change in tertiary structure of a self-protein would increase the risk of inducing antibody responses to sequentially native regions of the protein now having a changed structure, and not only to remaining native and amino acid sequence modified regions." Frøkjaer Declaration, at page 2, paragraph 3. Thus, Dr. Frøkjaer, one of at least ordinary skill in the art, understood the allegedly indefinite claim language to mean in functional terms[7]—adopting the Examiner's terminology—that a self-protein analog modified to include one or more foreign T cell epitopes had a preserved tertiary structure if it induced an auto-antibody response against the corresponding unmodified self-protein.

Next, Applicants submitted a Declaration by Dr. Paul Travers[8] on October 9, 2000, accompanying a Response to the Final Rejection mailed May 2, 2000. Dr. Travers noted that "[i]n paragraph 4 in the Office Action of 2 May 2000, the Examiner states that he finds the recitation of 'essentially preserve the overall tertiary structure' unclear. *It is my opinion as a skilled practitioner that this is not the case.*" Travers Declaration, at page 1, paragraph 4 (emphasis added). Dr. Travers further stated that "[i]t is my opinion that the wording 'essentially preserve [the] overall tertiary structure' as used in the above-captioned patent application can be readily be understood by the skilled reader."[9]

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[6] Dr. Frøkjaer worked for many years as a scientist both in the pharmaceutical industry and academia, and therefore is qualified at least as one of ordinary skill in the art, if not an expert. He was not affiliated with the current or former assignee of this application. *See* http://www.mva.org/content/us/about_us/board_of_directors/sven_frokjar.

[7] Applicants note that "[t]here is nothing inherently wrong with defining some part of an invention in functional terms. Functional language does not, in and of itself, render a claim improper." MPEP § 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971)).

[8] Dr. Travers worked for many years as an academic scientist, and therefore qualified at least as one of ordinary skill in the art, if not an expert. He was not affiliated with either the current or former assignee of this. Travers Declaration, at page 1, paragraph 1.

[9] According to Dr. Travers, the specification made clear that the 'essential preservation of overall tertiary structure' meant that "when a peptide containing a T-cell epitope is substituted into a self-protein according to the

(continued…)

Travers Declaration, at page 2, paragraph 6. Unfortunately, the Examiner essentially dismissed Dr. Travers' opinion, stating only that "[r]egarding applicants comments, said comments do not clarify what the term 'essentially preserve the overall tertiary structure' means or encompasses. In light of applicants comments it is still unclear what this means or encompasses. Regarding applicants comments about said term and preserving B cell epitopes, it is unclear what changes to the tertiary structure would or would not be encompassed by the aforementioned term." Advisory Action of February 21, 2001, section 6, page 3.

Most recently, Applicants submitted the Declaration of Alain Delcayre[10] under 37 C.F.R. § 1.132 ("Delcayre Declaration") with the Amendment and Reply filed November 24, 2010. Like Dr. Frøkjaer and Dr. Travers before him, Dr. Delcayre asserted that the meaning of the disputed claim language was clear. Indeed, based on the plain language of the claim and the disclosure of the specification, Dr. Delcayre understood that the secondary and tertiary structure of a self-protein analog is essentially preserved where: (1) the self-protein analog induces an autoantibody response in a subject; and (2) the induced autoantibodies bind to the corresponding unmodified self-protein. Delcayre Declaration, ¶¶5-6. The Examiner responded to the Delcayre Declaration in the same fashion as in previous Office Actions, by continuing to insist that it is unclear what sort of changes to the secondary and tertiary structure of the self-protein would be encompassed by the disputed

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(…continued)
above-captioned patent application, the substitution is one which introduces a minimum of disturbance in the tertiary structure of the self-protein whereby a maximum number of B-cell epitopes are preserved when comparing to the unmodified self-protein." Travers Declaration, at page 2, paragraph 6. Thus, Dr. Travers, a second person of at least ordinary skill in the art, understood the allegedly indefinite claim language to mean in functional terms—to adopt the Examiner's terminology—that a self-protein analog modified to include one or more foreign T cell epitopes had a preserved tertiary structure if the modification induced minimal tertiary structural changes in the native protein such that a maximum number of B-cell epitopes were preserved compared to the unmodified self-protein.

[10] Dr. Delcayre has conducted vaccine- and immunotherapy-related research for more than twenty years and therefore qualifies as one of at least ordinary skill in the art in those fields. He has been employed by the current assignee of the application since 2005. Delcayre Declaration, ¶¶1-2.

claim language—even though a third person of ordinary skill in the art again asserted that the meaning of that language was clear.

Thus, despite the fact that Applicants have repeatedly indicated throughout prosecution that the disputed claim term encompasses "functional changes"—adopting the Examiner's terminology—the Examiner continues to disregard that response and to insist that the claim term is indefinite because it is unclear whether the claim language encompasses "changes at the physical/chemical level or simply functional changes[.]"

Given the plain language of the claim, the Examiner's own understanding of the disputed claim term throughout prosecution, and the three separate Declarations by s having at least ordinary skill in the art all independently concluding that the disputed claim term is definite, it remains unclear to Applicants exactly why the Examiner continues to insist that it is unclear whether the claim language encompasses "changes at the physical/chemical level or simply functional changes[.]" Applicants reiterate that one skilled in the art would understand the disputed claim term to encompass 'functional changes' to the secondary and tertiary structure of a self-protein. Consequently, it is not necessary to define the nature and scope of the changes to the secondary and tertiary structure of the self-protein analog, despite the Examiner's repeated assertions to the contrary.

For this additional reason, Applicants respectfully assert that amended claims 102, 103, 105, and 111 comply with the definiteness requirement of 35 U.S.C. § 112, second paragraph, and therefore ask that the rejection be withdrawn.

V. Rejections under 35 U.S.C. § 103(a) (Obviousness).

A. Claim 102 over WO 92/05192, in view of US Patent No. 5,716,596 and US Patent No. 5,969,109.

The Examiner has rejected claim 102 under 35 U.S.C. § 103(a) as allegedly obvious over WO 1992/005192 ("Russell-Jones") in view of US Patent No. 5,716,596 ("Dean") and US Patent No. 5,969,109 ("Bona").

In particular, the Examiner alleged that Russell-Jones teaches "the claimed method except for the use of immunodominant foreign T cell epitopes derived from diphtheria toxoid[,]" that Bona teaches "that a T cell epitope can be substituted into a particular region of a target molecule wherein the T cell epitope retains immunogenicity[,]" and that Dean teaches that somatostatin is a self-protein because of its recognized role in a variety of diseases. Office Action mailed February 17, 2011, section 8, page 6. Based on those teachings, the Examiner concluded that "it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention[,]" and that a skilled artisan would have been motivated to combine those alleged teachings to arrive at the claimed invention "because immunodominant foreign T cell epitopes derived from diphtheria toxoid were known in the art and diphtheria toxoid was already approved as a carrier for human vaccines." *Id.*

Because the Examiner has mischaracterized Dean and Bona and failed to establish a *prima facie* case of obviousness as discussed in more detail below, Applicants respectfully traverse.

1. The Examiner has not established a *prima facie* case of obviousness because the cited references do not provide a motivation to combine the prior art to achieve the claimed invention.

To reject a claim as *prima facie* obvious under 35 U.S.C. § 103(a), the Examiner must show that "a person of ordinary skill in the art would have been motivated to combine the prior art to achieve the claimed invention and that there would have been a reasonable expectation of success." MPEP § 2143 (quoting *Dystar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d

1356, 1360 (Fed. Cir. 2006)). The Examiner has not met that burden, because the cited references do not provide a motivation to combine the prior art to achieve the claimed invention.

Patents and patent applications are relevant as prior art for all they disclose, and must be considered in their entirety, including portions that would teach away from the claimed invention. MPEP § 2123 (citing *In re Heck*, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (stating that patent references "are part of the literature of the art, relevant for all they contain")); *see also* MPEP § 2141.02(VI) (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983)).

a. Russell-Jones does not "teach the claimed method except for the use of immunodominant foreign T cell epitopes derived from diphtheria toxoid".

Russell-Jones does not "teach the claimed method except for the use of immunodominant foreign T cell epitopes derived from diphtheria toxoid," because the rejected claims recite "method[s] for inducing autoantibodies against a self-protein in a subject[.]" Virtually all of the disclosure in Russell-Jones contemplates raising immune responses against various immunogens by administration of immunogen-carrier conjugates where immunogens are attached to the carrier either by chemical coupling or by recombinant DNA methods (*i.e.*, fusion proteins). *See, e.g.*, Russell-Jones, at page 8, lines 30-35, and Abstract. The only disclosure even vaguely relating to the pending claims is a prophetic example describing the replacement of suppressor T-cell epitopes in a viral (*i.e.*, non-self) antigen with heterologous T-cell epitopes derived from TraT protein in an effort to stimulate an immune response against the immunosuppressive gp120 protein from type I human immunodeficiency virus ("HIV-1"). Russell-Jones, at page 31, Example 5. Because the antigen used—the HIV-1 gp120 protein—was derived from a foreign pathogen, any anti-gp120 antibodies induced by the gp120 analogue would not be autoantibodies. *Thus, Russell-Jones does not "teach the claimed method except for the use of immunodominant foreign T cell epitopes derived from diphtheria toxoid," because*

it does not teach or suggest methods for inducing autoantibodies against a self-protein in a subject by administering a self-protein analog made by substituting one or more peptide fragments in the self-protein with a corresponding number of immunodominant foreign T-cell epitopes.

b. Russell-Jones teaches away from the use of heterologous T-cell epitopes derived from DT or TT.

In fact, Russell-Jones actually teaches away from the use of heterologous T-cell epitopes derived from DT or TT, as discussed in more detail on pages 11-12 of the Amendment and Response filed November 24, 2010. Because Russell-Jones discloses: (1) that TraT conjugates and TraT-derived peptides induce a superior T-cell response compared to DT conjugates and DT-derived peptides; (2) that neither DT nor TT were selected for use as immunologic carriers because they had useful immunostimulatory characteristics; and (3) that commonly-used TT and DT carriers can lead to immunological complications, *the reference clearly teaches away from the use of DT conjugates or DT-derived peptides in vaccines or other immunotherapeutics.* Accordingly, Russell-Jones would not motivate one of ordinary skill in the art to combine its disclosure with that of Dean and Bona.

c. The disclosure of Dean and Bona does not remedy the deficiencies of Russell-Jones.

Even if the disclosure of Russell-Jones provided one of ordinary skill in the art the motivation to combine its disclosure with that of Dean and Bona—which Applicants assuredly **do not** concede for at least the reasons set forth above—the disclosure of Dean and Bona does not remedy the deficiencies of Russell-Jones.

The Examiner cited Bona for allegedly teaching "that a T cell epitope can be substituted into a particular region of a target molecule wherein the T cell epitope retains immunogenicity." Office Action mailed February 17, 2011, section 8, page 5. Bona describes the production of chimeric antibodies to which heterologous T- or B-cell epitopes have been added. Such antibodies are intended for use in methods of treating diseases caused by foreign pathogens (*e.g.*, influenza or HIV-

1) and for treatment of neoplasms. *Crucially, the heterologous epitopes are derived from foreign pathogens, and are used to stimulate or enhance a T- or B-cell response* ***directed to the chimeric antibody*** *(i.e., a non-self protein), rather than to induce the production of autoantibodies to a self-protein. See, e.g.*, Bona, col. 20:35 to col. 21:25. Thus, neither Russell-Jones nor Bona discloses methods of producing autoantibodies to self-proteins like the presently claimed methods.

The Examiner cited Dean simply for teaching that somatostatin is a self-protein because of its recognized role in a variety of diseases. Office Action, section 8, page 5. Dean describes the production of radiolabeled peptide derivatives and analogs of somatostatin for use as imaging and therapeutic agents, and does not mention vaccines at all. *See, e.g.*, Dean, col. 3:54-64.

Because neither Dean nor Bona remedies the deficiencies of Russell-Jones, the cited references do not provide one skilled in the art the motivation to combine the teachings of Russell-Jones, Dean, and Bona to arrive at the claimed invention. Consequently, the Examiner has not established a *prima facie* case of obviousness.

For at least this reason, Applicants respectfully ask that the rejection of claim 102 as allegedly obvious over WO 1992/005192, in view of US Patent No. 5,716,596 and US Patent No. 5,969,109, be withdrawn.

2. The Examiner has not established a *prima facie* case of obviousness because one of ordinary skill in the art would not have a reasonable expectation of success to arrive at the claimed invention by combining the cited references.

In addition, the Examiner has not established a *prima facie* case of obviousness because none of the cited references, either alone or in combination, provides **any** expectation of success—much less a reasonable expectation of success as required by section 2143 of the MPEP—to arrive at the claimed invention *because none of the references describes actually making a modified self-protein containing one or*

more T-cell epitopes substituted into the self-protein such that the secondary and tertiary structure of the self-protein is essentially preserved and using it to induce autoantibodies to the self-protein.

Thus, none of the cited references can provide any expectation that a modified self-protein made by substituting one or more peptide fragments in the self-protein with a corresponding number of immunodominant foreign T-cell epitopes would induce an autoantibody response to the unmodified self-protein as recited in the pending claims. Only Applicants' specification provides a reasonable expectation of success.

For at least this additional reason, Applicants ask that the rejection of claim 102 under 35 U.S.C. § 103(a) be withdrawn.

3. The rebuttal evidence of unexpected results is 'commensurate in scope with the claims which the evidence is offered to support.'

Finally, while Applicants have pointed out that the claimed invention has unexpected properties not present in the prior art, the Examiner observed that, according to MPEP § 716.02(d), "the 'objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support'" and alleged that the unexpected results discussed in the Amendment and Response filed January 22, 2010, and described in the specification are not commensurate in scope with the claimed invention, because the pending claims encompass methods of treating humans while the experiments disclosed in the specification were performed in mice. Office Action, section 8, page 8.

For at least the reasons set forth below, Applicants respectfully traverse.

a. The evidence of unexpected results need only be 'reasonably commensurate in scope with the claimed invention.'

To overcome a *prima facie* case of obviousness—which Applicants maintain the Examiner has not established, for at least the reasons discussed in Sections IV.A.1. and IV.A.2. above—rebuttal evidence of unexpected results need only be "reasonably commensurate in scope with the

claimed invention." MPEP § 2145 (citing *In re Kulling*, 897 F.2d 1147, 1149, 14 USPQ2d 1056, 1058 (Fed. Cir. 1990); *In re Grasselli,* 713 F.2d 731, 743, 218 USPQ 769, 777 (Fed. Cir. 1983)).Applicants maintain that the unexpected results discussed in the Amendment and Response filed January 22, 2010, and described in the specification are reasonably commensurate in scope with the claimed invention and "sufficient to establish a reasonable correlation between the showing and the entire scope of the claim, when viewed by a skilled artisan" for at least the reasons discussed in the Amendment and Response filed November 24, 2010. MPEP § 2145 (citing *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987); *Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980)).

During the telephone interview of April 27, 2011, however, the Examiner indicated that submission of data showing that the claimed methods also induce autoantibodies against self-protein analogues and self-protein-specific T-cell responses in humans might be sufficient to overcome this objection. Therefore, without acquiescing to the rejection, and solely to expedite prosecution, Applicants submit the accompanying Declaration of Fatema Legrand under 37 C.F.R. § 1.132 ("Legrand Declaration").

b. Data from two Phase I clinical trials shows that the claimed methods work in human cancer patients.

Dr. Legrand has conducted research in the fields of vaccines and immunology for more than a decade and therefore qualifies as one of ordinary skill in the art in those fields. Legrand Declaration, ¶¶1-2 and Exhibit 1. The Legrand Declaration reports the results of two clinical trials confirming the findings of the preclinical studies reported in the specification and indicating that

treatment of human cancer patients with a self-protein analogue modified according to the claimed methods overcame immune tolerance in the majority of patients.[11]

Dr. Legrand describes the results of two Phase I clinical trials administering a self-protein analog of Human Epidermal growth factor Receptor 2 ("HER2") made by substituting two peptide fragments in HER2 with a corresponding number of immunodominant foreign T-cell epitopes derived from tetanus toxin to human patients having metastatic HER2-overexpressing breast cancer. Legrand Declaration, ¶¶7-9. As Dr. Legrand explains, patients received vaccinations with a candidate breast cancer immunotherapy product designated MVA-BN®-HER2, comprising a highly attenuated vaccinia virus, MVA-BN®, engineered to encode a modified form of the HER2 protein, which is over-expressed in 20-30% of human breast cancers. *Id.*, at ¶7. MVA-BN®-HER2 encodes a modified form of the HER2 lacking its intracellular cell-signaling domain further modified to substitute two universal T-cell epitopes from tetanus toxin for amino acid sequences of the same length in the HER2 protein. *Id.* The T-cell epitopes facilitate the stimulation of an immune response to HER2, a self-protein, which requires the 'breaking' of immune tolerance (*i.e.*, the ability to distinguish self proteins from non-self proteins). *Id.*

Three groups of patients having HER2-overexpressing metastatic breast cancer were tested in the two fixed dose, single arm Phase I trials with the following treatments: (1) MVA-BN®-HER2 following first- or second-line chemotherapy alone (BNIT-BR-001, Cohort 1); (2) MVA-BN®-HER2 following first- or second-line chemotherapy in combination with single-agent taxane chemotherapy

[11] As is customary, preclinical studies generally examine a much wider range of biological responses to a particular therapeutic strategy than can be monitored in even a small clinical trial conducted in human patients, primarily for reasons of safety and cost. Legrand Declaration, at ¶6. For example, the clinical trials described by Dr. Legrand did not collect information regarding MHC haplotype of participating patients. *Id.* In addition, it is often impossible to replicate experimental conditions from preclinical studies in a clinical setting because patients enrolled in clinical trials are generally quite sick, and have in most cases been undergoing rigorous treatment with cytotoxic and immunosuppressive chemotherapeutics for some time. *Id.* That can present a significant challenge for trials of immunotherapies in the treatment of cancer, since many approved first-line chemotherapeutics have known immunosuppressive effects. *Id.*

(BNIT-BR-001, Cohort 2); and (3) MVA-BN®-HER2 following first- or second-line chemotherapy. Legrand Declaration, at ¶9. All patients from BNIT-BR-001 and BNIT-BR-002 were allowed to receive concurrent standard Herceptin® treatment, which was administered weekly according to the manufacturer's instructions. *Id.*, at ¶10. Patients from Cohort 2 of BNIT-BR-001 received concurrent standard Taxotere® (docetaxel) treatment administered every three weeks according to the manufacturer's instructions, given one week after or two weeks before MVA-BN®-HER2 treatments. *Id.*

Dr. Legrand further describes immune analysis of peripheral blood samples drawn from trial participants to measure humoral immune responses by enzyme-linked immunosorbent assay ("ELISA") and cellular immune responses by enzyme-linked immunosorbent spot assay ("ELISpot"). Legrand Declaration, at ¶12.

Vaccine-induced HER2-specific antibody responses were detected in 15 out of 29 patients (>50% response rate); subsequent analysis using a flow cytometry-based assay to characterize anti-HER2 antibody binding to HER2 expressing cells revealed responses in 2 additional patients having undetectable anti-HER-2 IgG ELISA. The difference in titers in pre- and post-treatment samples is highly statistically significant, supporting the conclusion that the increase in anti-HER2 titers observed is mediated by MVA-BN®-HER2 treatment. *Id.*, at ¶16. As expected, most patients (27 out of 30 or 90%) responded to MVA-BN®-HER2 treatment by mounting or boosting responses to the vaccine vector. *Id.*, at ¶18. Approximately one-third of the patients (9 out of 30) entered the study with a pre-existing MVA antibody titer. Of these, 7 out of 9 patients demonstrated a vaccine-induced boost in their anti-MVA titer post-vaccination. *Id.*

Overall, the trial results showed that, despite the immune-compromised status of the patients, MVA-BN®-HER2 was biologically active, inducing an antibody response against the HER2 transgene product in addition to the expected anti-vector responses. Importantly, pre-existing and

de novo response to the vaccine vector did not appear to affect the induction of anti-HER2 antibody responses. *Id.*, at ¶19.

Vaccine-induced HER2-specific T-cell responses to the HER2 extracellular domain ("ECD") were detected in five out of eight patients (63%) upon stimulation with at least one HER2 peptide reagent. Legrand Declaration, at ¶¶22-23. The fact that 63% of patients displayed vaccine-induced HER2-specific T-cell responses indicates immune activation of a broad population and substantiates the preclinical observation that MVA-BN®-HER2 responses are not MHC-restricted, since the most commonly occurring human MHC alleles appear at frequencies ranging from 29% to ~46%, depending on the population examined. Legrand Declaration, at ¶22; Exhibit 2, at Table 2; and Exhibit 3. Of those demonstrating a T cell response to the HER2-ECD reagent, two had pre-existing anti-HER2 T-cells that were significantly stimulated following treatment. However, in general the responses were modest (50-100 spots per 10^6 PBMC). At long-term follow-up, post treatment, HER2-specific T cell levels returned to baseline values. *Id.* Vaccine-induced responses (*de-novo* or an increase over pre-existing response) to the HER2 intracellular domain ("ICD") were detected in three out of eight patients evaluated upon stimulation with the HER2 ICD overlapping peptide library ("OPL"). *Id.*, at ¶¶24-25. Of the patients demonstrating a T cell response to the HER2-ICD reagent, two had a pre-existing HER2 ICD response that was significantly augmented and one showed a *de-novo* response to HER2 ICD. Induction of anti-HER2 ICD T-cell responses in the latter suggest possible epitope spreading to non-transgene determinants. *Id.* Strong MVA T cell responses were detected in 7 out of 8 patients tested prior to treatment that were all boosted following MVA-BN®-HER2 treatment. The only patient without detectable pre-existing anti-MVA T cells (07-033) developed a *de-novo* response to the vector upon treatment. At long-term follow-up, post treatment, MVA-specific T cell levels returned to baseline values. *Id.*, at ¶26.

These data corroborate the antibody data, as they confirm the potency of MVA-BN®-HER2 at inducing immune responses to both the HER2 transgene product and vector. As with the antibody responses, pre-existing and *de novo* responses to the vaccine vector did not appear to affect the induction of anti-HER2 T-cell responses. Legrand Declaration, at ¶26. Dr. Legrand concludes that the data presented above show that MVA-BN®-HER2 is immunogenic in human patients having HER2-overexpressing breast cancer. Legrand Declaration, at ¶27. Most importantly, MVA-BN®-HER2 immunogenicity was established based on the induction of immune responses to HER2, a self tumor antigen, a variant form of which is expressed by the viral vector. *Id.* Overall, anti-HER2 antibody and/or T-cell responses were detected in 19 out of 29 patients tested (66% response rate). Hence, MVA-BN®-HER2 treatment was able to break tolerance against HER2 in a majority of metastatic breast cancer patients, validating this compound as a vaccine candidate for cancer immunotherapy and confirming the findings of the preclinical studies reported in the specification. *Id.*

The human data described in the Legrand Declaration further supports Applicants' contention that the evidence of unexpected results in the specification is reasonably commensurate in scope with the claimed invention. For this additional reason, Applicants ask that the rejection of claim 102 under 35 U.S.C. § 103(a) be withdrawn.

B. Claim 111 over WO 92/05192, in view of US Patent No. 5,716,596 and US Patent No. 5,969,109, further in view of WO 93/05810 and US Patent No. 5,698,195.

The Examiner has rejected claim 111 under 35 U.S.C. § 103(a) as allegedly obvious over WO 1992/005192 ("Russell-Jones") in view of US Patent No. 5,716,596 ("Dean") and US Patent No. 5,969,109 ("Bona") as applied to claim 102 above, and further in view of WO 1993/005810 ("Hellman") and US Patent No. 5,698,195 ("Le"). In particular, the Examiner asserted that the rejection of claim 102 (*see* Section V.A. above) rendered obvious the claimed invention "except for

the use of TNFα[,]" but cited Hellman for allegedly teaching that "modulation of self-proteins responsible for manifestations of a particular disease can be achieved" by eliciting antibodies to a particular self-protein by administering the self-protein conjugated to a carrier comprising a T_H-cell epitope and Le for allegedly teaching that anti-TNFα antibodies can be used to treat TNFα-mediated diseases in humans. Office Action mailed February 17, 2011, section 9, page 8. The Examiner therefore concluded that "[i]t would have been *prima facie*[] obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention[.]" *Id.*

Applicants respectfully traverse for at least the reasons set forth in Section V.A. above regarding the rejection of claim 102 under 35 U.S.C. § 103(a). In addition, neither Hellman nor Le remedies the deficiencies of Russell-Jones discussed in detail above. Indeed, neither Hellman nor Le teaches or suggests substituting any of the T-cell epitopes recited in the pending claims as amended into a self-protein, or that a self-protein with a T-cell epitope substituted within it can induce an autoantibody response as shown by auto-antibody binding to the unmodified self-protein.

Consequently, the Examiner has not established a *prima facie* case of obviousness. Applicants therefore respectfully ask that the rejection of claim 111 as allegedly obvious over WO 1992/005192, in view of US Patent No. 5,716,596 and US Patent No. 5,969,109, further in view of WO 1993/005810 and US Patent No. 5,698,195 be withdrawn.

C. Claims 103 and 105 over WO 92/05192, in view of US Patent No. 5,716,596 and US Patent No. 5,969,109, further in view of US Patent Publication No. US 2003/0099634 A1.

The Examiner has rejected claims 103 and 105 under 35 U.S.C. § 103(a) as allegedly obvious over WO 1992/005192 ("Russell-Jones") in view of US Patent No. 5,716,596 ("Dean") and US Patent No. 5,969,109 ("Bona") as applied to claim 102 above, and further in view of US Patent Publication No. US 2003/0099634 A1 ("Vitiello"). In particular, the Examiner asserted that the rejection of claim 102 (*see* Section V.B. above) rendered obvious the claimed invention "except for

use of the ovalbumin epitope recited in claim 105[,]" but cited Vitiello for allegedly teaching an immunogenic peptide comprising the ovalbumin epitope and concluded that "[i]t would have been *prima facie*[] obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention[.]" Office Action mailed February 17, 2011, section 10, page 9.

Applicants respectfully traverse for at least the reasons set forth in Section V.A. above regarding the rejection of claim 102 under 35 U.S.C. § 103(a). In addition, Vitiello does not remedy the deficiencies of Russell-Jones discussed in detail above. That is, Vitiello does not teach or suggest substituting any T-cell epitope into a self-protein such that the secondary and tertiary structure of the self-protein is essentially preserved. Moreover, Vitiello does not teach or suggest substituting any of the T-cell epitopes recited in the pending claims as amended into a self-protein, or that a self-protein with a T-cell epitope substituted within it can induce an autoantibody response as shown by auto-antibody binding to the unmodified self-protein.

Consequently, the Examiner has not established a *prima facie* case of obviousness. Applicants therefore respectfully ask that the rejection of claims 103 and 105 as allegedly obvious over WO 1992/005192, in view of US Patent No. 5,716,596 and US Patent No. 5,969,109, further in view of US Patent Publication No. US 2003/0099634 A1 be withdrawn.

VI. Conclusion.

In view of the amendments and remarks presented above, Applicants believe that each of the presently pending claims is in condition for allowance. Accordingly, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims. If the Examiner determines that a telephone conference would expedite prosecution of this application, Applicants invite the Examiner to telephone the undersigned at the number listed below.

In the event that the United States Patent & Trademark Office ("USPTO") determines that an extension of time or other relief is required, Applicants hereby petition for any relief including extensions of time, and authorize the Commissioner of the USPTO to charge the cost of such petitions and/or any other fees due in connection with the filing of this document to **Deposit Account No. 50-5338**, referencing **Docket No. BNIT0003-PCT-US**. However, the Commissioner is not authorized to charge the Issue Fee to the Deposit Account.

Respectfully submitted,

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